Consanguinity and Recurrence Risk of Stillbirth and Infant Death

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ABSTRACT

Objectives. The aim of this study was to estimate the recurrence risk for stillbirth and infant death and compare results for offspring of first-cousin parents with results for offspring of unrelated parents.

Methods. The study population consisted of all single births with a previous sibling born in Norway between 1967 and 1994. Altogether, 629 888 births were to unrelated parents, and 3466 births were to parents who were first cousins. The risk of stillbirth and infant death was estimated for subsequent siblings contingent on parental consanguinity and survival of the previous sibling.

Results. For unrelated parents, the risk of early death (stillbirth plus infant death) for the subsequent sibling was 17 of 1000 if the previous child survived and 67 of 1000 if the previous child died before 1 year of age. For parents who were first cousins, the risk of early death for the subsequent sibling was 29 of 1000 if the previous child survived and 116 of 1000 if the previous child died.

Conclusions. The risk of recurrence of stillbirth and infant death is higher for offspring of first-cousin parents compared with offspring of unrelated parents. (*Am J Public Health.* 1999:89:517–523)

In many countries, between 20% and 60% of marriages are consanguineous (Table 1).[1–12] Consanguinity has a significant influence on child mortality and morbidity independent of other causes of death and disease.[13,14] Previous studies of mainly nonconsanguineous parents have found that once stillbirth or infant death has appeared in a family, the risk of recurrence in subsequent siblings is higher than the population risk.[15,16] However, it is not obvious that the risk of recurrence is higher for infants whose parents are consanguineous compared with infants whose parents are unrelated.

Most studies on consanguinity and recurrence of disease or death have focused on particular recessive diseases within a single family.[17,18] In 1965, Schull and Neel reported a comprehensive population-based study on the effects of inbreeding in Japanese children; recurrence risk for serious malformations in siblings was estimated on the basis of information on 99 pairs of siblings with unrelated parents and 424 pairs with first-cousin parents.[19] To our knowledge, no previous population-based studies on the recurrence risk of stillbirth or infant death have compared children of consanguineous and unrelated parents.

Estimates of recurrence risk help clinicians understand the etiology of stillbirth and infant death. These estimates provide a measure of the aggregation of stillbirth and infant death within consanguineous and nonconsanguineous families, and they are useful in genetic counseling, particularly when the specific etiology of death is uncertain. However, estimation of population-based recurrence risks of early death requires large study populations because only children with a previous sibling can be included. Most previous studies on consanguinity and stillbirth or infant death have been too small to calculate recurrence risks for siblings.[20,21]

Although consanguineous marriages are rare in Norway, the Norwegian Medical Birth Registry provides a unique opportunity to study recurrence of stillbirth and infant death among children of consanguineous and unrelated parents. All births in Norway have been recorded with information on the biological relationship between parents, and the number of children with consanguineous parents has increased over the last 30 years because of immigration from countries where consanguineous marriages are common.

Most previous studies on recurrence risk have limited analyses to data for the first- and second-born child to avoid bias from selective fertility.[22] In contrast, the present study covers a total population and includes a large number of births by consanguineous parents. With adjustment for sibling number, we have been able to use data on all births for siblings. In addition, the results are adjusted for maternal age, educational levels of the parents, and year of birth.

The purpose of this study was to estimate the recurrence risk of stillbirth and infant death among subsequent siblings who have either first-cousin parents or unrelated parents. Parental consanguinity increases the probability of homozygosity at any given chromosomal locus for the offspring. The core research hypothesis is that consanguinity leads to a higher risk of recurrence, and the effect of consanguinity is stronger when the previous sibling was stillborn or died as an infant because of the increased proportion of

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homozygosity for disease-associated genes among offspring of consanguineous parents.

Methods

Study Population

The Medical Birth Registry of Norway has recorded all births of longer than 16 weeks' gestation since 1967.[23] These registry data were linked to information from Statistics Norway on cause of death and parental educational levels. Siblings with the same parents were linked through the identification numbers of their parents. After exclusion of plural births, all births within a sibship were numbered chronologically. All births with a previous sibling (sibling number 2 or higher) were included in the analysis.

Early Death

The outcome variables were stillbirth, infant death, and early death. Throughout the analyses, we used the concept of risk rather than the more commonly used concepts of stillbirth rate and infant mortality rate.[24] The risk of stillbirth is defined as the probability of death before and during delivery for all births with a gestational age of 16 weeks or more. The risk of infant death is defined as the probability of death in the first year of life for live births. The risk of early death is the combined probability of stillbirth and infant death. In this study, risk is expressed as number of deaths per 1000 births or live births.

Previous Early Death

Stillbirth or infant death of the previous sibling was a main explanatory variable. The survival of the previous child was a variable characterizing the subsequent child. Consequently, the risk of early death in sibling number 2 was analyzed according to the survival of sibling number 1, whereas the risk of death in sibling number 3 was analyzed according to the survival of sibling number 2, and so forth. We use the terms *older sibling* synonymously with *previous sibling* and *younger sibling* synonymously with *subsequent sibling.*

Consanguinity

Parental consanguinity was the other main explanatory variable. Only sibships with parents who were unrelated (nonconsanguineous) or first cousins (consanguineous) were included in the analyses. Sibships with parents for whom information on consanguinity was missing (0.1%) or who were registered as biologically related other than as first cousins (1.4%) were excluded. A couple who was recorded to be first cousins for at least 1 of the children in a sibship was considered as consanguineous for all of their children. We use the terms *consanguineous* synonymously with *first cousin* and *nonconsanguineous* synonymously with *unrelated.*

TABLE 1—Frequency of Consanguineous Marriages in Selected Populations

Country and Population	Consanguinity, % First-Cousin Marriages	Consanguinity, % All Consanguineous Marriages	Reference
United Kingdom			
Immigrants from Pakistan	40.0[a]	69.0	2
Pakistan	49.4	61.6	3
United Arab Emirates	31.5	61.6	4
Iraq	30.0	57.9	5
Saudi Arabia	28.4	57.7	6
Kuwait	32.2	54.3	7
Jordan	35.4	50.2	8
Norway			
Immigrants from Pakistan	37.7	48.3	Data in present study
Bahrain	21.0	39.4	9
Egypt	14.1	29.0	10
Lebanon			
Muslims	17.3	29.6	11
Christians	7.9	16.5	11
Turkey	7.2	21.2	12
Norway			
Ethnic Norwegian	0.1	1.3	Data in present study
Immigrants from countries other than Pakistan	3.1	5.2	Data in present study

[a]40.0 were reported to be more closely related than first cousins.

Sibling Number, Maternal Age, Parental Educational Levels, and Year of Birth

The following covariates were included in the study: sibling number, maternal age, parental educational levels, and year of birth. Sibling number was categorized as 2, 3, or 4 and higher. Mother's age at delivery was classified into 3 categories: younger than 20 years, 20 through 29 years, and 30 years or older. Mother's and father's number of years of education completed by 1990 was obtained from a census conducted by Statistics Norway in 1990. Years of education were divided into less than 13 and 13 or more. Parents with missing information on educational levels were included in the group with the lowest educational level. The year of birth of the child was assigned to 1 of 3 categories: 1967 to 1975, 1976 to 1984, and 1985 to 1994. The effects of the main explanatory variables were adjusted for sibling number, maternal age, parental educational levels, and year of birth in the multivariate excess risk models described below and in the estimation of relative risks.

Recurrence Risk, Excess Risk, and Relative Risk

Recurrence risk of stillbirth and infant death is defined as the conditional probability of death given that the previous sibling was stillborn or died before 1 year of age. Excess risk is defined as a difference between 2 absolute risks. Excess risks are presented as the difference between the risk to subsequent siblings with unrelated parents and a previous sibling who survived (group A) and the risk to subsequent siblings with 1 of the following: first-cousin parents and a previous sibling who survived (group B), unrelated parents and a previous sibling who was stillborn or died before 1 year of age (group C), and first-cousin parents and a previous sibling who was stillborn or died before 1 year of age (group D) (Tables 2–4). Excess risks and relative risks for the effects of previous death (recurrence risk: comparing risk group D with B, and C with A) and consanguinity (comparing risk group D with C, and B with A) are presented in the text.

Statistical Methods

The risk of early death was estimated for births with unrelated and first-cousin parents dependent on survival of the previ-

TABLE 2—Numbers, Risks, and Adjusted Excess Risks of Early Deaths Among Subsequent Siblings According to Parental Consanguinity and Survival of the Previous Sibling: Norway, 1967–1994

Risk Group	First-Cousin Parents	Early Death of Previous Sibling	No. of Births With a Previous Sibling	No. of Early Deaths Among Subsequent Siblings	Risk of Early Death: No. of Deaths/1000 Births (95% Confidence Interval)	Adjusted Excess Risks: No. of Deaths/1000 Births (95% Confidence Interval)
A	–	–	613307	10405	17 (17, 17)	
B	+	–	3320	96	29 (24, 35)	10 (5, 16)
C	–	+	16581	1111	67 (63, 71)	48 (44, 52)
D	+	+	146	17	116 (64, 168)	95 (43, 148)
All			633354	11629	18 (18, 19)	

Note. A = unrelated parents and a previous sibling who survived; B = first-cousin parents and a previous sibling who survived; C = unrelated parents and a previous sibling who was stillborn or died before 1 year of age; D = first-cousin parents and a previous sibling who was stillborn or died before 1 year of age.

ous sibling (Table 2). In addition, the risks of stillbirth and infant death were estimated dependent on previous stillbirth and infant death, yielding the combinations shown in Tables 3 and 4.

We used additive models to estimate adjusted excess risks for the main explanatory variables.[25] The excess risk models can be described by the following formula:

$$P(Y_i = 1|B_i,C_i,D_i,\mathbf{x}_i) = \alpha + \beta_1 B_i + \beta_2 C_i + \beta_3 D_i + \gamma \mathbf{x}_i$$

In this formula, Y_i represents the outcome variable (stillbirth or infant death) for subject *i*. B_i, C_i, and D_i denote group membership for subject *i* in the risk groups described above. α is the risk for group A. β_1, β_2, and β_3 are the adjusted excess risks for risk groups B, C, and D, respectively. $\mathbf{x}_i$ is a vector of covariates (sibling number, mother's and father's educational levels, and year of birth) with corresponding parameter vector γ.

In addition to the excess risks estimated in the additive model, we have estimated approximate relative risks as adjusted odds ratios (ORs) with 95% confidence intervals (CIs) in logistic regression models.[26]

Both the excess risk and the relative risk models were estimated by maximum likelihood with EGRET software.[27] Confidence intervals for adjusted excess risks, adjusted relative risks, and interactions were calculated based on Wald-statistics. Cross-tabulations were conducted with SPSS.[28]

Results

There were 633354 births with a previous sibling, among whom 6345 were stillborn and 5284 died as infants. In 8185 births, a previous sibling was stillborn, and in 8542, a previous sibling died as an infant.

The risks and the adjusted excess risks of early death for the subsequent sibling are presented in Table 2. The risks for the 4 combinations of stillbirth and infant death are presented in Tables 3 and 4, and the corresponding adjusted excess risks are shown in Tables 5 and 6.

Early Death

For first-cousin parents, the risk of early death for the younger sibling was higher than for unrelated parents when the first child survived (Table 2). The relative risk associated with consanguinity was similar for first-cousin parents whose previous child survived until 1 year of age (risk group B relative to A; adjusted OR = 1.6, 95% CI = 1.3, 1.9) and those whose previous child died early (risk group D relative to C; adjusted OR = 1.7, 95% CI = 1.0, 2.8). The corresponding adjusted excess risks associated with consanguinity were 10/1000 and 47/1000, respectively. Similarly, the relative risks associated with the early death of a previous child were almost identical for first-cousin parents (risk group D relative to B; adjusted OR = 3.9, 95% CI = 2.3, 6.9) and for unrelated parents (risk group C relative to A; adjusted OR = 3.8, 95% CI = 3.6, 4.1). Again, the corresponding adjusted excess risks differed considerably, with a value of 86/1000 for the consanguineous group vs 48/1000 for the unrelated group. The excess risk for first-cousin parents with a previous child who died early was higher than the sum of the individual excess risks for consanguinity and death of a previous child. However, the interaction between the 2 risk factors on the additive scale was not statistically significant.

Stillbirth and Infant Death

Tables 3 and 4 show the numbers and risks of stillbirth and infant death for the subsequent child by parental consanguinity and survival of the previous sibling. For first-cousin parents, the risk of stillbirth was slightly higher than for unrelated parents if the previous child was not stillborn. The risk of infant death was clearly higher for first-cousin parents than for unrelated parents if the previous child had survived the first year of life. For first-cousin parents, the risk of recurrence of stillbirth was 111/1000 births and of recurrence of infant death was 77/1000 live births, which was considerably higher than the respective risks for unrelated parents.

The influence of having a previous child who died was stronger than the influence of parental consanguinity for all 4 combinations of outcomes in the previous and the subsequent sibling. Consanguinity had a relatively stronger effect on infant death than on stillbirth, whereas the effect of death of the previous child was highest for like outcomes (stillbirth–stillbirth, infant death–infant death). The risk of recurrence of stillbirth or infant death in the subsequent sibling was higher for consanguineous than for unrelated parents, except for the combination of previous infant death and subsequent stillbirth, which could not be evaluated because there was only 1 death.

Tables 5 and 6 list the adjusted excess risks associated with parental consanguinity or previous early death or both, compared with the risks of those who had unrelated parents and a previous sibling who was live born or had survived the first year of life.

Previous stillbirth and subsequent stillbirth. Consanguinity had no independent significant effect on occurrence of stillbirth in the subsequent child, whereas the effect of a previous stillbirth was stronger than for any other combination of outcomes. The excess risk associated with the combined effect of parental consanguinity and stillbirth in the previous sibling was considerably greater than the sum of the independent risk factors. However, this interaction was not statistically significant (adjusted point estimate = 48/1000; 95% CI = –36/1000, 132/1000).

Previous infant death and subsequent stillbirth. Infant death in the previous child

TABLE 3—Numbers and Risks of Stillbirths Among Subsequent Siblings According to Parental Consanguinity and Survival Till Birth of the Previous Sibling: Norway, 1967–1994

Risk Group	Consanguinity	Previous Sibling Was Stillborn	No. of Births	No. of Stillbirths	Risk of Stillbirth: Stillbirths/ 1000 Births (95% Confidence Interval)	No. of Live Births	No. of Infant Deaths	Risk of Infant Death: Infant Deaths/1000 Live Births (95% Confidence Interval)
A	–	–	621757	5818	9 (9, 10)	615939	5029	8 (8, 8)
B	+	–	3412	45	13 (10, 18)	3367	59	18 (13, 23)
C	–	+	8131	476	59 (53, 64)	7655	193	25 (22, 29)
D	+	+	54	6	111 (42, 226)	48	3	63 (13, 172)

Note. A = unrelated parents and a previous sibling who survived; B = first-cousin parents and a previous sibling who survived; C = unrelated parents and a previous sibling who was stillborn; D = first-cousin parents and a previous sibling who was stillborn.

significantly influenced the risk of stillbirth in the subsequent child. The combined effect of parental consanguinity and infant death in the previous child was difficult to evaluate because only 1 child in this group was stillborn.

Previous stillbirth and subsequent infant death. Parental consanguinity significantly affected the excess risk of infant death in the subsequent child. A previous stillborn sibling was associated with an increased risk of infant death in the subsequent child, although not as much as for stillbirth. The combination of a previous stillbirth and parental consanguinity increased the risk of infant death considerably but only half as much as it increased the risk of a subsequent stillbirth. Again, the point estimate for the interaction indicated synergy but was not statistically significant (adjusted point estimate=29/1000 live births; 95% CI=–40/1000, 97/1000).

Previous infant death and subsequent infant death. The excess risk of infant death increased significantly when the previous sibling had died as an infant. When the parents were first cousins and the previous child had died as an infant, the risk of infant death for the subsequent child was greater than the sum of the separate effects of parental consanguinity and previous infant death. This excess risk was exceeded only by the excess risk for stillbirth. The excess risk due to the interaction between consanguinity and previous infant death indicated synergy but was not significant (adjusted point estimate=38/1000 live births; 95% CI=–17/1000, 93/1000).

Influence of Sibling Number, Maternal Age, Parental Educational Levels, and Year of Birth

The excess risks and the relative risks associated with parental consanguinity and previous death were not appreciably altered by sibling number, maternal age, parental educational levels, and year of birth on either stillbirth or infant death (Tables 5 and 6). Sibling number was significantly associated with both stillbirth and infant death. However, no interactions occurred between sibling number and previous stillbirth or infant death or between sibling number and parental consanguinity. Thus, all pairs of older and younger siblings could be analyzed simultaneously independent of sibling number.

Discussion

In this study, we have estimated population-based recurrence risks for stillbirth and infant death for siblings with unrelated and first-cousin parents and adjusted for the effects of parental educational levels and other factors that influence the risk of stillbirth and infant death. Consanguinity leads to a higher risk of recurrence, and the effect of consanguinity is higher when the previous sibling was stillborn or died as an infant.

Recurrence Risk and Modes of Inheritance

Stillbirth and infant death have heterogeneous etiologies that are subject to secular changes and vary within and between populations. With the exception of known recessive and dominant genetic diseases with full penetrance, expected recurrence risks are unknown. On the basis of theoretical calculations, it has been postulated that all other causes of death tend to produce lower recurrence risks than do dominant and recessive genes, including environmental factors that are correlated in families.[29]

A major aim of inbreeding studies is to establish the influence of genetic factors in disease and to assess the relative contribution of genetic and environmental causes of disease and death.[30] Consanguineous parents have children with an increased probability of being homozygous at any given gene

TABLE 4—Numbers and Risks of Infant Deaths Among Subsequent Siblings According to Parental Consanguinity and First-Year Survival of the Previous Sibling: Norway, 1967–1994

Risk Group	Consanguinity	Previous Sibling Died as an Infant	No. of Births	No. of Stillbirths	Risk of Stillbirth: Stillbirths/ 1000 Births (95% Confidence Interval)	No. of Live Births	No. of Infant Deaths	Risk of Infant Death: Infant Deaths/1000 Live Births (95% Confidence Interval)
A	–	–	621438	6110	10 (10, 10)	615328	4964	8 (8, 8)
B	+	–	3374	50	15 (11, 20)	3324	55	17 (13, 21)
C	–	+	8450	184	22 (19, 25)	8266	258	31 (28, 35)
D	+	+	92	1	11 (0, 59)	91	7	77 (31, 152)

Note. A = unrelated parents and a previous sibling who survived; B = first-cousin parents and a previous sibling who survived; C = unrelated parents and a previous sibling who died before 1 year of age; D = first-cousin parents and a previous sibling who died before 1 year of age.

TABLE 5—Excess Risks of Stillbirth With 95% Confidence Intervals (CIs) for Subsequent Siblings, Dependent on Parental Consanguinity and Survival Till Birth of the Previous Sibling: Norway, 1967–1994

Comparison	Risk Group: First-Cousin Parents	Risk Group: Previous Sibling Was Stillborn	Compared With	Risk Group: First-Cousin Parents	Risk Group: Previous Sibling Was Stillborn	Stillbirths/1000 Births, Adjusted Excess Risk (95% CI)	Infant Deaths/ 1000 Live Births, Adjusted Excess Risk (95% CI)
B–A	+	–		–	–	3 (–1, 6)[a]	9 (5, 13)[b]
C–A	–	+		–	–	48 (43, 53)[c]	16 (12, 19)[d]
D–A	+	+		–	–	99 (15, 183)[e]	53 (–15, 122)[f]

Note. Risks adjusted for sibling number, maternal age, mother's and father's educational levels, and year of birth. Father's education was not included in the model for stillbirth contingent on infant death in the previous sibling. A = unrelated parents and a previous sibling who survived; B = first-cousin parents and a previous sibling who survived; C = unrelated parents and a previous sibling who was stillborn; D = first-cousin parents and a previous sibling who was stillborn.

[a]Consanguinity had no independent significant effect on occurrence of stillbirth in the subsequent child.
[b]Parental consanguinity significantly affected the excess risk of infant death in the subsequent child.
[c]The effect of a previous stillbirth was stronger than for any other combination of outcomes.
[d]A previous stillborn sibling was associated with an increased risk of infant death in the subsequent child.
[e]The excess risk associated with the combined effect of parental consanguinity and stillbirth in the previous sibling was considerably greater than the sum of the independent risk factors.
[f]The combination of a previous stillbirth and parental consanguinity increased the risk of infant death considerably.

locus, and, in general, studies on consanguinity can be used to evaluate the influence of homozygosity in any condition. Traditionally, it is assumed that the main cause of differences in risk between consanguineous and nonconsanguineous groups is recessive diseases.[15] However, diseases with polygenic etiology contribute, and homozygosity for dominant disease also may play a role.[15,31] Homozygotes of dominant disorders may be more severely affected and have an earlier onset than heterozygotes of dominant disorders.[31] Most conditions and diseases are a result of interaction between environmental and genetic factors, and homozygosity for an allele associated with disease may alter the influence of environmental factors involved in development of the disease.[32]

Once a birth defect, a stillbirth, or the death of an infant has occurred in a family, it is not obvious that the recurrence risk should be greater for children with consanguineous parents. For any given recessive or dominant disease, the recurrence risk in the consanguineous and nonconsanguineous groups should, theoretically, be similar. The recurrence risks for monogenic autosomal dominant and recessive diseases with no heterogeneity and full penetrance are 50% and 25%, respectively, although even in these disorders, there may be more genetic complexity than expected.[33–35] Recurrence risks for multifactorial diseases have been estimated based on the assumptions of additive effects of genes and environmental factors, a continuous underlying liability, and a critical threshold level for disease.[36,37] According to Bonaiti,[38] recurrence risks in multifactorial inheritance for siblings with first-cousin parents are only slightly higher than recurrence risks for those with unrelated parents.

In conclusion, the recurrence risks of subsequent siblings whose older siblings died early would be similar in the consanguineous and the unrelated groups if the causes of early death had been distributed similarly in the 2 groups. Here, the adjusted excess risks are different, indicating the influence of the increased homozygosity among offspring of first-cousin parents. Population-based recurrence risks among children with consanguineous and nonconsanguineous parents may provide a basis for theoretical modeling of the effects of disease-associated genes in heterozygous and homozygous states.

TABLE 6—Excess Risks of Infant Death With 95% Confidence Intervals (CIs) for Subsequent Siblings, Dependent on Parental Consanguinity and First-Year Survival of the Previous Sibling: Births in Norway, 1967–1994

Comparison	Risk Group: First-Cousin Parents	Risk Group: Previous Sibling Died as an Infant	Compared With	Risk Group: First-Cousin Parents	Risk Group: Previous Sibling Died as an Infant	Stillbirth, Adjusted Excess Risk (95% CI)	Infant Death, Adjusted Excess Risk (95% CI)
B–A	+	–		–	–	4 (0, 8)[a]	8 (4, 12)[b]
C–A	–	+		–	–	11 (8, 15)[c]	21 (18, 25)[d]
D–A	+	+		–	–	1 (–20, 22)[e]	68 (13, 122)[f]

Note. Risks adjusted for sibling number, maternal age, mother's and father's educational levels, and year of birth. Father's education was not included in the model for stillbirth contingent on infant death in the previous sibling. A = unrelated parents and a previous sibling who survived; B = first-cousin parents and a previous sibling who survived; C = unrelated parents and a previous sibling who died before 1 year of age; D = first-cousin parents and a previous sibling who died before 1 year of age.

[a]Consanguinity had no independent significant effect on occurrence of stillbirth in the subsequent child.
[b]Parental consanguinity significantly affected the excess risk of infant death in the subsequent child.
[c]Infant death in the previous child significantly influenced the risk of stillbirth in the subsequent child.
[d]The excess risk of infant death increased significantly when the previous sibling had died as an infant.
[e]The combined effect of parental consanguinity and infant death in the previous child was difficult to evaluate because only one child in this group was stillborn.
[f]The parents were first cousins and the previous child had died as an infant.

Excess Risk and Relative Risk

In this study, relative recurrence risks were similar, whereas excess risks of recurrence differed for the consanguineous and the unrelated group. By definition, relative risks are dependent on the occurrence of the condition in the control group representing the general, or nonconsanguineous, population and will therefore necessarily be lower when baseline rates are higher. Consequently, analysis of the effects of inbreeding should not rely solely on the comparison of relative risks. An analysis of excess risks of prereproductive death for offspring of first-cousin parents concluded that the absolute effect of consanguinity was constant across a wide range of population risks of prereproductive death.[39] In a recent study from Pakistan, the relative risk of infant death for children with first-cousin parents was lower than in a study of children of Pakistani origin in Norway (ORs = 1.3 and 2.1, respectively), whereas the excess risk of infant death was approximately 18/1000 in Pakistan and 12/1000 in Norway (authors' calculations).[3,14]

A methodology for estimating excess risks, adjusting for other variables, was developed in the present analysis of recurrence risks. Hence, adjusted excess risks may complement adjusted relative risks as measures of association and indeed show effects that cannot be measured as relative risks.

Data Quality

Possible biases that could have influenced the results of this study include systematic differences between the consanguineous and the unrelated group and differences in the ascertainment of consanguinity, stillbirth, and infant death.

Immigrants are overrepresented among parents who are first cousins (64.6%), but they constitute only 4.7% of all parents in the Medical Birth Registry. An earlier study based on data from the Norwegian Medical Birth Registry found that the risk of early death was equal for children with first-cousin parents, independent of ethnic origin, and that the risk of stillbirth and infant death for children with unrelated parents did not vary significantly among ethnic groups.[14] Analysis of the present data, including ethnic group as a covariate, did not alter the results significantly. Thus, for the purpose of the present study, data from all ethnic groups could be pooled.

Consanguinity is routinely recorded on a standardized form when the mother undergoes her first routine examination for pregnancy, usually before 12 weeks of gestation. The ascertainment of infant death and late stillbirth (28 weeks of gestation or more) is high in the Norwegian Medical Birth Registry because of established linkage with the Cause of Death Registry. We included early stillbirths (16–28 weeks of gestation) to increase the number of recurrences. No known biological reason indicates that stillbirths should be included only from week 28 on while live births are included independent of gestational age, and there are no indications of differential misclassifications of early stillbirth between consanguineous and unrelated parents.[14]

Sibling number, maternal age, parental educational level, and year of birth have significant effects on stillbirth and infant death.[3,22,40–42] However, the effects of parental consanguinity and previous death on recurrence risk persisted after adjustment for these covariates. Residual confounding by factors not included in the model, such as interpregnancy interval, could explain some of the excess risk associated with consanguinity. However, the stability of the effects of consanguinity across time and ethnic groups indicates that the possible residual confounding in the present study is minimal.[13,14]

Interaction

No statistically significant interactions were found between parental consanguinity and death of the previous sibling on the additive scale, probably as a result of low statistical power.[43] Death of the previous sibling was dealt with as an exposure in this analysis. We did not assume that death of the previous sibling was the cause of the death of the subsequent sibling or a modifier of risk through biological interaction. Rather, we assumed that the death of a previous child was an expression of underlying risk factors. One such risk factor is consanguinity.

Public Health Implications

The results of the present study have public health implications because consanguinity is prevalent globally.[1] The aggregation of stillbirths and infant deaths is stronger in consanguineous families than in families with unrelated parents, which is important for the distribution of burden of disease and death in populations. In individual genetic counseling, estimates of recurrence risk are needed. However, they should be used with caution and only when more specific knowledge of etiology is not available. Consanguineous marriage has cultural and economic advantages, and knowledge of the advantages and the risks associated with consanguinity is essential to decisions about public health measures.

Conclusion

Consanguinity influences the risk and recurrence risk of stillbirth and infant death. An aggregation of early death occurs in certain families, and the strength of this aggregation is higher when the parents are first cousins than when they are unrelated. □

Contributors

C. Stoltenberg planned the study, organized the linkage of the registry data, analyzed the data, and wrote the paper. P. Magnus supervised the study closely at all stages. A. Skrondal designed the statistical method, wrote the section on statistics, and supervised the analysis. R. Terje Lie supervised the study at all stages. All 4 authors are guarantors for the integrity of the research.

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